48.001

Antimycobacterial activity of pyrimido[4,5-*b*]diazepine derivatives

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Background: Human tuberculosis is a contagious-infectious disease mainly caused by *Mycobacterium tuberculosis*, which is an aerobic pathogenic bacterium that establishes its infection usually in the lungs. About one third of the world's population is currently infected with *M. tuberculosis*; 10% of those infected will develop clinical disease, particularly those who also have the human immunodeficiency virus (HIV) infection. This problem is further compounded by a dramatic increase in multidrug-resistant strains of *M. tuberculosis* which demands the search for alternative antimycobacterial drugs. In this effort, diazepine derivatives, which showed a broad spectrum of biological activity especially antitumoral is presented as a promising source of new compounds-leaders. Using the existing capacity that posses the Colombian National Institute of Health (NIH) for to develop reproducible *in vitro* tests against mycobacteria species and the research trajectory of Grupo de Investigación de Compuestos Heterocíclicos, the aim of this study was to determine the activity against 15 *Mycobacterium* spp strains and clinical isolates of 12 diazepine derivatives.

Methods: The synthesis of pyrimidodiazepines by microwave irradiation (200 °C, 300 W) during 2-8 minutes of equimolar mixture of 2-R-4,5,6-triamino-pyrimidines and chalcones in DMF (0.5 mL) and catalytic amount of BF3.OEt2 (0.5 mL. The minimum inhibitory concentration (MIC) was determined by colorimetric broth microdilution method. The activity was evaluated against five *M. tuberculosis* ATCC strains, 5 isolates of Beijing genotype and 5 clinical isolates of nontuberculous mycobacteria. Isoniazid and rifampicin were used as control drugs.

Results: In total six diazepine derivatives showed moderate activity at concentrations in a range between 16-32 μg/mL (Good activity CMI <10 μg/ mL), three were active against 13 microorganisms; the rest just inhibited the growth of *M. tuberculosis* strains.

Conclusion: Diazepine derivatives scaffolds over the years have gained an ongoing interest for biological activities as anticancer, anti-bacterial, psychotropics, anti-convulsant, anti-viral, and herbicidal. This is the first report of antimycobacterial activity of diazepine compounds developed entirely in Colombia, in addition, also includes multidrug-resistant isolates classified in the national resistance studies conducted in the Colombian National Institute of Health (NIH).

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Five year trend of antimicrobial susceptibility rates and daptomycin activity among *Staphylococcus aureus* isolates collected in Latin American medical eenters (2005-2009)

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Background: Daptomycin is lipopeptide with a unique mechanism of action and rapid bactericidal activity against Gram-positive cocci. Daptomycin is approved for the treatment of Gram-positive pathogen associated complicated skin and skin structure infections (cSSSI) and *S. aureus* (SA)-associated bacteremia and endocarditis and in the United States, Europe and some Latin American (LA) countries. The in vitro activity of daptomycin and comparator agents was evaluated against clinical isolates of SA collected in four LA countries over five years.

Methods: 6,031 SA isolates were collected in 10 medical centers located in Argentina (1,075), Brazil (2,637), Chile (1,345) and Mexico (974). Isolates were mainly from bloodstream (42.1%) and cSSSI (28.6%). Susceptibility (S) was determined by the CLSI broth microdilution method in cation-adjusted Mueller-Hinton broth supplemented to 50 mg/L of calcium for daptomycin tests.

Results: The overall oxacillin resistance (MRSA) rate in LA was 41.1% and ranged from 32.1-39.0% in Brazil and Mexico to 51.7-51.9% in Argentina and Chile. MRSA rates increased continuously from 34.7 (2005) to 48.4% (2009). Daptomycin was highly active against SA in all LA countries with MIC50 and MIC90 values of 0.25 and 0.5 mg/ml, respectively. Overall, daptomycin was highly active against MRSA (100.0% S, see table) as was vancomycin (MIC50/90, 1/1 mg/ml; 100% S) and linezolid (MIC50/90, 1/2 mg/ml; >99.9% S). Erythromycin resistance was higher in Chile and Mexico (46.5-54.5%) than in Argentina and Brazil (38.2-39.4%). Overall constitutive clindamycin resistance was 78.8% in LA. TMP/SMX and tetracycline resistance was much higher in Brazil (20.6-23.6%) compared to other countries (1.5-6.2%). Levofloxacin and gentamicin resistance was highest in Chile at 52.1% and 42.8%, respectively.

Nation (no. of SA strains)	Cumulative % inhibited at daptomycin MIC (μg/ml) of:					
	≤0.06	0.12	0.25	0.5	1	2
Argentina (1,075)	0.0	2.3	62.1	98.5	100.0	-
Brazil (2,637)	0.1	2.1	61.1	98.4	100.0	-
Chile (1,345)	0.2	2.8	57.3	97.9	100.0	-
Mexico (974)	0.5	3.9	74.6	99.2	99.9	-
All regions						
Methicillin-S (3,552)	0.2	3.3	77.3	99.1	>99.9	100.0
MRSA (2479)	0.1	1.5	41.6	97.5	100.0	-

Conclusion: Significant resistance variations among SA and several classes of antimicrobial agents were observed in LA countries. Daptomycin showed consistent potency against recent clinical isolates of SA collected in LA medical centers, including MDR strains. Resistance to other compounds did not adversely influence daptomycin potency and with S rates at over 99.9% during the past five years suggests that daptomycin has maintained in vitro activity in LA countries.

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48.003

In vitro activity of new compound YF-13-1 against gram-postive and gram-negative bacteria strains of clinical isolates in chain

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Background: The Present study is undertaken to evaluate and compared the activity of the new compound YF-13-1 alone and with eight antibiotics against gram — positive and gram — negative. Bacterial strains. The majority of bacterial strains evaluated in this study were recent clinical isolates obtained from several hospital sources in China.

Methods: Determination of antibacterial activity in vitro: Minimum inhibitory concentrations (MICs) were determined according to CLSI(formerly NCCLs guidelines using cation — adjusted Mueller-Hinton agar.) by the agar dilution method with a Multiple innoculator replicator (steers-folty replicator) serialtwofold dilutions of the compounds will be prepared 10-fold in agar, ranged from 128 to 0.008 ug/ml (for extremely sensitive organisms, further dilutions).the lowest concentration which allowed the growth of no more than three colonies is considered to be the MICs.

Results: The results showed that YF-13-1 was a broad-Spectrum Antibiotics. MIC50, MIC90 values for YF-13-1 were each 0.25 mg/L and 1 mg/L against ciprofloxacin-susceptible and levofloxacin- susceptible S.aureus strains. It inhibited 90% tested Ciprofloxacin and levofloxacin- resistant S. aureus strains at less than 16 mg/L. MIC 90 values against S. aureus MRSA, MSSA was 4 mg/L, 0.25 mg/L respectively. YF-13-1 was more active against coagulose-negative. Staphylococci and S.epidermidis MRSE, MSSE, MIC90 were 1 mg/L, 8 mg/L; 2 mg/L and 0.25 mg/L respectively. MIC90 was)4 mg/L against S.pyogenes, S.pneumoniae and Enterococccus. MIC 90 4, 8, 0.5 mg/L against Branhemella bacteria, influengae and Gonococcal respectively. Whereas, the YF-13-1 MIC range for E.coli, K. peumoniae, Proteus, Serratia marcescens, E. aerogenes and cloacae were 0.008- 32 mg/L. MIC50, MIC90 was 2 mg/L and 8 mg/L against P. aerogenes respectively, But, it less active against acinetobacter baumannii, MIC50, MIC90 was 8 mg/L, 128 mg/L respectively.

Conclusion: The results showed that YF-13-1 was a broad-Spectrum Antibiotics.

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48.004

10-hydroxy-2-decenoic acid induce dispersion of *Streptococcus mutans* biofilms

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Background: Hydroxy decenoic acid is a bioactive component of royal jelly that occupies its 10% of the total weight. Biofilms progress through multiple developmental stages, beginning with reversible attachment to a surface, followed by irreversible attachment and development of microcolonies, when dispersion occurs, releasing cells into the bulk liquid. Colonization and Biofilm formation of *Streptococcus mutans* is the causative agent of dental plaques and subsequently dental caries.

Methods: 10-hydroxy decenoic acid was purified by means of HPLC. Glass slides were used for biofilm formation in treated media with each slide in a total area of 6 cm2. Microtiter plate dispersion bioassays were used to test various preparations for their ability to exogenously induce *Streptococcus mutans* ATCC 25175 biofilm dispersion.

Results: Hydroxy decenoic acid is capable of inducing the dispersion of established biofilms and of inhibiting biofilm development. When added exogenously to *Streptococcus mutans* biofilms at a native concentration of 2.5 nM, it was shown to induce the dispersion of biofilm microcolonies. These dispersion events were observed to originate at the center of microcolonies near the substratum, but only within microcolonies that had attained a minimum diameter of 40 μ and a minimum thickness of 10 μm.

Conclusion: Active at nanomolar concentrations, hydroxy-2-decenoic acid appears to be functionally and structurally related to the class of short-chain fatty acid signaling molecules such as diffusible signal factor, which act as cell-to-cell communication molecules in bacterial colonies.

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